Please add the following new claims:

–20. A composition for treating acne, comprising a compatible combination of: a neutrophil elastase inhibitor; and an active ingredient selected from the group consisting of comedolytics, antibacterials, anti-inflammatories, retinoids, glucocorticoids, and compatible mixtures thereof.–

A3

–21. The composition of claim 1, further comprising as an active ingredient an antibacterial.–

REMARKS

Entry of the foregoing amendments, and reexamination and reconsideration of the subject application, pursuant to and consistent with 37 C.F.R. § 1.104 and § 1.112, and in light of the following remarks, are respectfully requested.

Claim 1 has been amended to incorporate the limitations of claim 2, which is now cancelled, that the inhibitor in the first instance is not an "antioxidant," and that the active ingredient is not an antibacterial. Claim 9 has been amended to recite the composition as "further comprising" an antioxidant. New claim 20 is directed specifically to neutrophil elastase inhibitors (*e.g.*, paragraph bridging pages 15-16 of the application for exemplary neutrophil elastase inhibitors). New no matter is added.

Rejections under 35 U.S.C. 102

Claims 1-9 stand rejected hereunder as anticipated by Oliver, Murad, Ramamurthy, or Liu, which rejections are respectfully traversed.

Oliver discloses a "skin treatment" composition allegedly useful for everything from acne (caused by bacteria), to athlete's foot (caused by fungus), to skin bites (caused by insects and arachnids), rashes of unknown or undefined etiology, and the like. On its face, these types of allegations are unbelievable and unscientific (see Dr. Kang's Declaration under Rule 132 in connection with the rejections below). Nevertheless, Oliver discloses the use of the antioxidant

Vits. C and E. As now amended, claim 1 requires an MMP inhibitor that is not an antioxidant. Accordingly, these claims are not anticipated by Oliver.

Murad discloses an oral composition for removing wrinkles that includes Vit. C, NAC, and optional ingredients including various vitamins or quercetin. There is no mention of acne by Murad, and no mention of MMP inhibitors of any kind, especially none that are non-retinoid and non-antioxidant. Accordingly, these claims are not anticipated by Murad.

Ramamurthy discloses the combination of a bisphosphonate and tetracycline for everything from treating AIDS to osteoporosis to burns to periodontal disease (top of column 3). Acne is not mentioned. The statement in the Office Action that bisphosphonates are "elastase" inhibitors is incorrect; they are MMP inhibitors, not elastase inhibitors (note also col. 6, ln. 34-40, wherein Ramamurthy describes transition metals as elastase inhibitors). Further, as now amended, claim 1 requires an active ingredient selected from comedolytics, anti-inflammatories, retinoids, glucocorticoids, not requiring an antibacterial (although one can be added later, as per new claim 21). Accordingly, Ramamurthy does not anticipate the present claims.

Finally, Liu is directed solely to a storage stable vehicle for a retinoid, which can accomodate a multitude of optional ingredients. The examiner's reference to "example 3 at column 10" appears to be incorrect, and clarification is requested. Regardless, none of the combinations of presently claimed inhibitors and active ingredients is disclosed by Liu; all of the Liu compositions presumably have a retinoid, but none appear to have a non-retinoid, non-antioxidant inhibitor of a dermal matrix-degrading enzyme. Accordingly, Liu does not anticipate the present claims.

Rejection under 35 U.S.C. 103

Claims 10-19 stand rejected over the combination of Teronen and Ramamurthy, which rejection is respectfully traversed.

As an aside, claims 18-19 depend on claim 1, not claim 10, and so appear to have been rejected improperly for this particular rejection.

Substantively, the rejection alleges that the different routes of administration, oral retinoid plus topical MMP inhibitor, would have been obvious to one of ordinary skill in the art.

First, although Ramamurthy mentions acne, he provides no evidence that there is any "extracellular protein degradation," even though such disclosure is in the background section of the patent. It is the present inventors who were the first to discover the activity of MMPs in acne. A search at the National Library of Medicine website (MEDLINE/PubMed via http://www.nlm.nih.gov/hinfo.html) using "acne" and "MMP" as the search terms pulled up only three references, none of which address acne treatment using MMP inhibitors in combination with conventional acne therapy.

Second, Ramamurthy requires the compounds (tetracycline plus bisphosphonate) to be administered together:

> The amounts of the tetracycline and the bisphsphonates useful in the invention are amonts which in combination result in an inhibition of the activity and/or secretion and synthesis of excess proteinase in a system or subject susceptible to excess proteinases. These amounts are advantageously as much as ten-fold less than amounts which are optimal or needed when each compound is used alone, thereby significantly reducing the possibility of side effects caused by higher doses if the compounds were taken individually.

(Col. 8, ln. 43-53.) All of the experiments in columns 9 and 10 describe administering both compounds together by the same route of administration. The citation in the rejection (to col. 8) that the amounts of the compounds can be varied, depending on the route of adminstration, does not teach different routes of administration, especially because that section discusses "each compound in the composition" and "the site to which the composition is administered."

Thirdly, Ramamurthy teaches that both antibacterial and non-antibacterial tetracyclines are suitable. Ramamurthy teaches using "chemically modified

tetracyclines," CMTs, which are not antibacterial: col. 3, ln. 41-55, for non-antimicrobial tetracyclines as MMP inhibitors; col. 4, ln. 33-64, for specific CMTs; bottom of col. 7, teaching both antibacterial and non-antibacterial tetracyclines as suitable; and col. 9, ln. 59-67 ("[these] experiments demonstrate that a combination of a chemically-modified non-antibacterial tetracycline plus a bisphosphonate synergistically inhibits connective tissue . . . breakdown"). Thus, Ramamurthy teaches away from using only antibacterial tetracyclines.

Fourth, enclosed is a Declaration under Rule 132 from Dr. Kang explaining why one of ordinary skill in the dermatological arts would disbelieve the teachings in Ramamurthy as applied to skin conditions. As Dr. Kang notes, he is only opinining on the dermatological conditions mentioned by Ramamurthy, which raises additional questions as to what relationship of *all* of the conditions mentioned by the reference what have (for none is described by the reference). More specifically, the various skin conditions mentioned by Ramamurthy are not related, each has different treatment and a different cause, and none were known to involve MMPs. For example, epidermolysis bullosa (EB) has two forms, a congenital form that is not curable, and an acquired form that is treated with immunosuppressive drugs; Ramamurthy does not even show an appreciation for these two forms, whether they are or are not related, and why his invention is supposedly suitable for both? or one? (and if one, why not the other). The examples in Ramamurthy do not treat any skin conditions, and they use rats (there is no animal model for acne).

While Teronen teaches bisphosphonates used in combination with other drugs, there is no example of a combined therapy, except perhaps Prophetic Example 4, where it is in a toothpaste, and assuming fluoride is the other active ingredient, again the ingredients are co-administered.

Dr. Kang's Declaration also notes that the Teronen disclosure of conditions for which that invention functions is virtually the same as that of Ramamurthy, and the disclosure is similarly lacking.

Thus, Ramamurthy uses MMP-inhibiting tetracyclines, which can be non-antibiotic, and the MMP inhibitor bisphosphonate, and so is not concerned with using antibiotic tetracycline. Teronen adds little to Ramamurthy.

The advantage in the present invention of topical and oral administration is that each of the separate effects can be treated separately. Neither of these references provides any motivation for different routes of administration; each is directed to decreasing MMPs, so that is the effect desired. In contrast, in acne, as the present inventors have found, after the bacterial infestation by *P. acnes*, there is a secondary effect of MMP induction, which likely varies among patients. The claimed method requires treating both the bacterial infection and the increased levels of MMPs; hence, while administering a conventional oral acne medication one can topically administer an MMP inhibitor only as required. This treatment aspect is not appreciated by either of the references.

Under *Graham v. John Deere Co.*, 383 U.S. 1, 148 U.S.P.Q. 459 (1966), an inquiry under 35 U.S.C. 103 must include interpretation of the prior art by one of ordinary skill in the pertinent art. It cannot be assumed that a patentee is one of ordinary skill in the art; in fact, the patentee need not have any skill in the art. Given the lack of disclosure in the Ramamurthy and Teronen references relating to dermatology, it can be inferred easily that those patentees are not skilled in the dermatological arts. Rather, Dr. Kang is at least closer to the level of one of ordinary skill in the art than the patentees of the cited references. Accordingly, Dr. Kang's declaration brings into question both what each of these references teaches one of ordinary skill in the art, and thus the motivation for applying either of these references to the problem of treating acne.

The allegation in the rejection that combination therapies are popular and so modifying the route of administration "to find the best combination fits in patient's need and for most effective therapy" is an improper 'obvious to try' standard. That the separate ingredients in a combination therapy could be administered by different routes does not teach or provide reasoning or motivation for doing so. In fact, patient compliance is a key issue for any

treatment, and so the protocol is to provide all medications in a single composition to facilitate patient compliance (*i.e.*, the patient only has to take one pill or use one cream, and does not have multiple bottles and/or tubes). Accordingly, the claimed method would not have been obvious.

Obviousness-type Double Patenting

All of the claims stand rejected hereunder as obvious variants of the '394, '224, or '254 patents. This rejection is respecfully traversed.

First, regarding the method claims directed to treating acne, the claims of the '224 and '254 patents are directed to preventing photoaging. In *Ex parte Zbornik*, 109 U.S.P.Q. 508 (B.P.A.I. 1956), the applicant recited administering a compound to fowl suffering from a specific condition. The compound was old, its use in fowl was old, and its route of administration was old. Yet the Board found

> . . . no merit in this rejection because in holding that [the reference] substantially meets the claims the examiner is obviously giving no weight to the limitation in the claims that the medicated feed is administered to fowls infected with Air Sac Infection. He [the examiner] thus fails to follow the long line of decisions in which it was held that in evaluating the patentability of process claims the "material acted upon" must be given weight.

Id. at 509. In *Zbornik* the Board thus held effectively that "fowls infected with Air Sac Infection" was the material acted upon. Ergo, the condition of the patient treated, and the results intended by such treatment, provide the context to be used when evaluating a *method* claim. Thus, the methods recited in the '224 and '254 claims do not render obvious the claimed method.

As for the composition claims, there is nothing in the '224 or '254 patent claims that would suggest the need to use a non-retinoid, non-antioxidant MMP inhibitor in combination with a conventional acne therapy. Also, while the rejection mentions the use of Vit. C in the '254 patent, such is now eliminated fromclaim 1.

While the compositions in the '394 patent could be used in the present invention to reduce the amount of a retinoid (if such is used), those claims lack any recitation of a non-retinoid, non-antioxidant MMP inhibitor.

Accordingly, the claims are not obvious variants of those patent claims.

Conclusion

In light of the foregoing, withdrawal of the rejections, and further and favorable action, in the form of a Notice of Allowance, are believed to be next in order, and such actions are earnestly solicited.

Petition for Extension of Time

Pursuant to the provisions of 37 CFR 1.136(a), Applicants hereby petition for a one month extension of time to 10 September 2001 in order to respond to the Office Action dated 10 May 2001. ~~A check in the amount of $ 110.00 is attached~~. If this paper should necessitate any fees under 37 C.F.R. § 1.16 or § 1.17 not provided, or if there has been an overpayment, please debit or credit as necessary the firm's Deposit Account No. 08-2776.

Respectfully submitted,

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Dated: 10 September 2001

CERTIFICATE OF MAILING OR TRANSMISSION – 37 CFR 1.8

I hereby certify that I have a reasonable basis that this paper, along with any referred to above, (i) are being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to Commissioner of Patents and Trademarks, Washington, D.C. 20231, or (ii) are being transmitted to the U.S. Patent & Trademark Office in accordance with 37 CFR § 1.6(d).

DATE: 9/10/01

NAME: Heather A. McLennand

SIGNATURE: Heather A. McLennand

APPENDIX SHOWING MARK-UPS OF AMENDMENTS

1. (Amended.) A composition for alleviating acne scarring, comprising a compatible combination of: a non-retinoid, non-antioxidant inhibitor of a dermal matrix-degrading enzyme, said inhibitor selected from the group consisting of AP-1 inhibitors, NF-κB inhibitors, elastase inhibitors, adhesion antagonists, and mixtures thereof; and an active ingredient selected from the group consisting of comedolytics, [antibacterials,] anti-inflammatories, retinoids, glucocorticoids, and compatible mixtures thereof.

Cancel claim 2.

9. (Amended.) The composition of claim 1, wherein the inhibitor [is] further comprises an antioxidant.